PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 50821-15 PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/10639	International filing date *(day/month/year)* 07 April 2004 (07.04.2004)	Priority date *(day/month/year)* 07 April 2003 (07.04.2003)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 239/36, 239/91 and US Cl.: 544/287, 319		
Applicant NPS PHARMACEUTICALS, INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 18 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05 November 2004 (05.11.2004)	25 July 2005 (25.07.2005)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Dorothea Lawrence for Deepak Rao Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/10639

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:
pages 1-17 as originally filed/furnished
pages* 18-27 received by this Authority on 05 November 2004 (05.11.2004)
pages* NONE received by this Authority on _____

☒ the claims:
pages NONE as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* 28-35 received by this Authority on 05 November 2004 (05.11.2004)
pages* NONE received by this Authority on _____

☐ the drawings:
pages NONE as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/10639

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 5-17, 22-37, 41-42	YES
	Claims 1-4, 18-21, 38-40	NO
Inventive Step (IS)	Claims 5-17, 22-37, 41-42	YES
	Claims 1-4, 18-21, 38-40	NO
Industrial Applicability (IA)	Claims 1-42	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-4, 18-21 and 38-40 lack novelty under PCT Article 33(2) as being anticipated by US 5,378,678. The instantly claimed method of preparing pyrimidin-4-one compounds reads on the reference disclosed method, see the reaction taught in col. 5, lines 62-67 of the reference.

Claims 1-4, 18-21 and 38-40 lack an inventive step under PCT Article 33(3) as being obvious over US 5,378,678. The reference teaches a method of preparing pyrimidin-4-one compounds, see the reaction scheme in col. 5, lines 62-67. One of ordinary skill would have been motivated to modify the reference method to prepare the claimed compounds with the reasonable expectation of obtaining structurally analogous compounds from the analogous process.

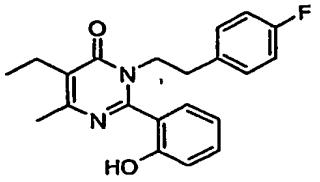
Claims 5-17, 22-37 and 41-42 meet the criteria of novelty and inventive step set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a method comprising the steps recited in these claims. The reference does not specifically teach or fairly suggest the intermittent steps to prepare pyrimidin-4-one compounds.

Claims 1-42 meet the criteria set out in PCT Article 33(4) because the claimed method is disclosed to be useful in preparing biologically active compounds, and thus meet the requirement of industrial applicability because the subject matter claimed can be made or used in industry.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

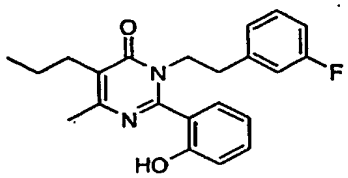


[0068] Utilizing the procedures described in Example 1a-g except substituting 2-ethyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 4-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 51% after crystallization from hexanes - ethyl acetate (5:1).

[0069] ^{1}H NMR ($CDCl_3$): δ 7.15 (dt, 1H, J_1 = 8.0, J_2 = 1.5), 7.06 (dd, 1H, J_1 = 7.8, J_2 = 1.5), 6.80 - 6.70 (m, 6H), 4.04 (t, 2H, J = 7.5), 2.78 (t, 2H, J = 7.5), 2.55 (q, 2H, J = 7.5), 2.24 (s, 3H), 1.10 (t, 3H, J = 7.5).

Example 9

Preparation of 3-[2-(3-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-5-propyl-3*H*-pyrimidin-4-one



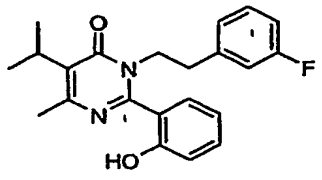
[0070]Utilizing the procedures described in Example 1a-g except substituting 2-propyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 3-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 12% after two crystallization from hexanes - ethyl acetate (10:1).

[0071]^{1}H NMR ($CDCl_3$): δ 9.72 (broad s, 1H), 7.19 - 7.04 (m, 3H), 6.87 - 6.81 (m, 2H), 6.76 (d, 1H, J = 8.2), 6.63 (dd, 1H, J = 7.8), 6.50 (dt, 1H, J_1 = 8.2, J_2 = 1.8), 4.09 (t, 2H, J = 7.2), 2.82 (t, 2H, J = 7.2), 2.50 (t, 2H, J = 8.2), 2.25 (s, 3H), 1.53 (m, 2H), 0.98 (t, 3H, J = 7.2).

[0072] ^{13}C NMR ($CDCl_3$): δ 162.95 (d, J = 243), 162.67, 157.25, 156.04, 154.85, 140.28 (d, J = 7.2), 132.10, 130.15 (d, J = 8), 129.19, 124.57 (d, J = 2.4), 123.82, 120.65, 119.95, 117.73, 115.77 (d, J = 21), 113.72 (d, J = 21), 47.69, 34.16, 28.55, 21.60, 20.85, 14.48.

Example 10

Preparation of 3-[2-(3-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one



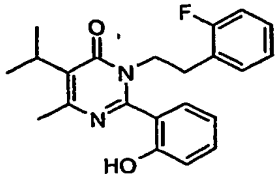
[0073] Utilizing the procedures described in Example 1a-g except substituting 2-isopropyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 3-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 52% after crystallization from hexanes - ethyl acetate (10:1).

[0074] ^{1}H NMR ($CDCl_3$): δ 7.21 - 7.09 (m, 3H), 6.85 (m, 2H), 6.76 (d, 1H, J = 8.1), 6.65 (d, 1H, J = 7.4), 6.52 (dd, 1H, J_1 = 8.1, J_2 = 1.5), 4.09 (t, 2H, J = 7.4), 3.10 (p, 1H, J = 7.0), 2.85 (t, 2H, J = 7.4), 2.27 (s, 3H), 1.35 (d, 6H, J = 7.0).

[0075] ^{13}C NMR ($CDCl_3$): δ 162.95 (d, J = 244), 161.70, 156.05, 155.19, 140.30 (d, J = 7), 132.15, 130.16 (d, J = 8), 128.98, 127.84, 124.57 (d, J = 2), 120.24, 119.85, 117.91, 115.78 (d, J = 21), 113.73 (d, J = 21), 47.47, 34.118, 28.24, 21.41, 19.68.

Example 11

Preparation of 3-[2-(2-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one



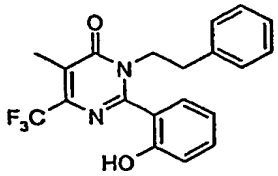
[0076] Utilizing the procedures described in Example 1a-g except substituting 2-isopropyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 2-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 50% after crystallization from hexanes - ethyl acetate (10:1).

[0077] ^{1}H NMR ($CDCl_3$): δ 10.10 (broad s, 1H), 7.20 - 7.10 (m, 2H), 7.04 (dd, 1H, J_1 = 7.7, J_2 = 1.6), 6.94 - 6.73 (m, 5H), 4.13 (t, 2H, J = 7.0), 3.10 (m, 1H), 2.94 (t, 2H, J = 7.0), 2.28 (s, 3H), 1.35 (d, 6H, J = 6.9).

[0078] ^{13}C NMR ($CDCl_3$): δ 161.81, 161.34 (d, J = 244), 156.14, 155.98, 158.26, 131.92, 131.34 (d, J = 4.5), 129.08, 128.65 (d, J = 7.8), 127.68, 124.76 (d, J = 16), 124.27 (d, J = 3.3), 120.00, 119.72, 117.46, 115.45 (d, J = 21.6), 46.31, 28.16, 27.85, 21.44, 19.67.

Example 12

Preparation of 2-(2-Hydroxy-phenyl)-5-methyl-3-phenethyl-6-trifluoromethyl-3*H*-pyrimidin-4-one



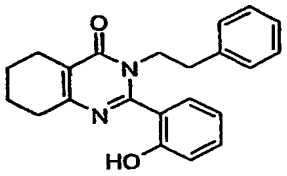
[0079] Utilizing the procedures described in Example 1a-g except substituting 2-trifluoromethyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a the title compound was prepared. Yield 20 % after three crystallizations from hexanes - ethyl acetate (2:1).

[0080] ^{1}H NMR ($CDCl_3$): δ 10.31 (s, 1H), 7.42 (m, 1H), 7.19 (m, 3H), 7.13 (dd, 1H, J_1 = 7.6, J_2 = 1.6), 7.01 (d, 1H, J = 7.9), 6.93 (m, 1H), 6.78 (m, 2H), 3.98 (t, 2H, J = 7.8), 2.79 (t, 2H, J = 7.8), 2.22 (q, 3H, J = 2.2).

[0081] ^{13}C NMR ($CDCl_3$): δ 162.05, 156.90, 153.88, 144.91 (q, J = 32), 137.61, 131.74, 129.66, 128.57, 128.33, 126.60, 122.40, 121.76 (q, J = 275), 121.40, 119.22, 115.76, 47.50, 33.17, 10.78.

Example 13

Preparation of 2-(2-Hydroxy-phenyl)-3-phenethyl-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one



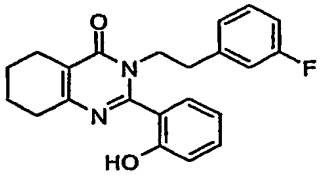
[0082] Utilizing the procedures described in Example 1a-g except substituting 2-oxo-cyclohexanecarboxylic acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a the title compound was prepared. Yield 55% after crystallization from hexanes - ethyl acetate (1:1).

[0083] ^{1}H NMR ($CDCl_3$): δ 10.00 (broad s, 1H), 7.14 - 7.00 (m, 5H), 6.80 – 6.69 (m, 4H), 4.02 (t, 2H, J = 7.4), 2.79 (t, 2H, J = 7.4), 2.5 (m, 4H), 1.68 (m, 4H).

[0084] ^{13}C NMR ($CDCl_3$): δ 162.42, 158.75, 156.29, 154.30, 137.87, 131.77, 129.36, 128.86, 128.59, 126.63, 121.33, 120.73, 119.85, 117.18; 47.60, 34.55, 30.79, 22.62, 21.97, 21.66.

Example 14

Preparation of 3-[2-(3-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one



[0085] Utilizing the procedures described in Example 1a-g except substituting 2-oxo-cyclohexanecarboxylic acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl

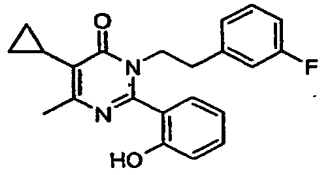
ester in step 1a and 3-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 56% after crystallization from hexanes - ethyl acetate (1:1).

[0086] ^{1}H NMR ($CDCl_3$): δ 10.10 (broad s, 1H), 7.15 - 7.02 (m, 3H), 6.78 – 6.81 (m, 2H), 6.70 (d, 1H, J = 8.1), 6.61 (d, 1H, J = 7.7), 6.46 (d, 1H, J = 8.1), 4.06 (t, 2H, J = 7.0), 2.79 (t, 2H, J = 7.0), 2.51 (m, 4H), 1.72 (m, 4H).

[0087] ^{13}C NMR ($CDCl_3$): δ 162.92 (d, J = 244), 162.42, 158.63, 156.27, 154.38, 140.30 (d, J = 7.3), 132.10, 130.14 (d, J = 8.3), 129.34, 124.57 (d, J = 2.2), 121.18, 120.85, 120.15, 118.02, 115.76 (d, J = 20.7), 113.70 (d, J = 21), 47.34, 34.25, 30.83, 22.68, 22.02, 21.71.

Example 15

Preparation of 5-Cyclopropyl-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one



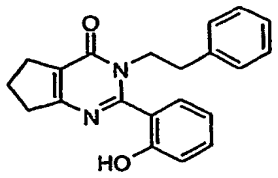
[0088] Utilizing the procedures described in Example 1a-g except substituting 2-cyclopropyl-3-oxo-butyric acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 3-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 56% after crystallization from hexanes - ethyl acetate (1:1).

[0089] ^{1}H NMR ($CDCl_3$): δ 9.70 (broad s, 1H), 7.31 (m, 1H), 7.15 (m, 2H), 6.91 (m, 3H), 6.70 (m, 1H), 6.59 (m, 1H), 4.25 (t, 2H, J = 7.6), 2.90 (t, 2H, J = 7.6), 2.38 (s, 3H), 1.61 (m, 1H), 0.99 (m, 2H), 0.87 (m, 2H).

[0090] ^{13}C NMR ($CDCl_3$): δ 162.77 (d, J = 245), 162.35, 159.27, 156.16, 154.91, 140.05 (d, J = 7.3), 132.10, 129.97 (d, J = 8.1), 128.83, 124.34 (d, J = 2.3), 122.95, 120.02, 119.82, 118.17, 115.55 (d, J = 21), 113.56 (d, J = 21), 47.40, 34.03, 21.22, 8.81, 6.64.

Example 16

Preparation of 2-(2-hydroxy-phenyl)-3-phenethyl-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one



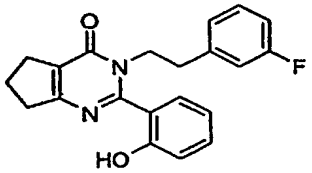
[0091] Utilizing the procedures described in Example 1a-g except substituting 2-oxo-cyclopentanecarboxylic acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a the title compound was prepared. Yield 52% after crystallization from hexanes - ethyl acetate (1:1).

[0092] ^{1}H NMR ($CDCl_3$): δ 9.12 (broad s, 1H), 7.17 (m, 5H), 6.85 (m, 4H), 4.18 (t, 2H, *J* = 7.8), 2.84 (m, 6H), 2.08 (m, 2H).

[0093] ^{13}C NMR ($CDCl_3$): δ 166.59, 160.72, 158.96, 154.47, 137.61, 131.87, 128.98, 128.70, 128.51, 126.58, 123.61, 120.88, 119.86, 117.75, 47.58, 34.57, 34.33, 27.83, 21.32.

Example 17

Preparation of 3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one



[0094] Utilizing the procedures described in Example 1a-g except substituting 2-oxo-cyclopentanecarboxylic acid ethyl ester for 2-methyl-3-oxo-butyric acid ethyl ester in step 1a and 3-fluoro-phenethylamine for phenethylamine in step 1c the title compound was prepared. Yield 51% after crystallization from hexanes - ethyl acetate (1:1).

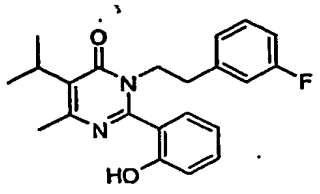
[0095] ^{1}H NMR ($CDCl_3$): δ 9.41 (broad s, 1H), 7.23 (m, 1H), 7.11 (m, 2H), 6.86 (m, 3H), 6.65 (d, 1H, *J* = 7.6), 6.51 (d, 1H, *J* = 9.6), 4.18 (t, 2H, *J* = 7.7), 2.84 (m, 6H), 2.09 (m, 2H).

[0096] ^{13}C NMR ($CDCl_3$): δ 166.95, 162.74 (d, *J* = 245), 160.64, 159.01, 154.20, 140.07 (d, *J* = 7.4), 131.88, 129.96 (d, *J* = 8.1), 128.99, 124.36, 123.61, 121.10,

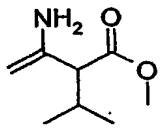
119.86, 117.40, 115.56 (d, J = 21), 113.53 (d, J = 21), 113.53 (d, J = 21), 47.14, 34.29, 34.19, 27.78, 21.29.

Example 18

Preparation of 3-[2-(3-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one

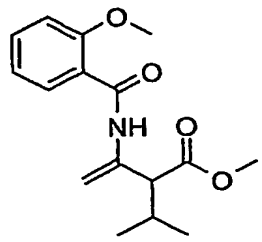


a). 3-Amino-2-isopropyl-but-3-enoic acid methyl ester.



[0097] 2-Methyl-3-oxo-butyric acid methyl ester (10 g, 0.0633 mol) was dissolved in absolute ethanol (50 mL). Excess of liquid ammonia (10 fold) was added and the mixture was stirred at room temperature in a sealed reaction vessel for 48 h. Excess ammonia and ethanol were removed under reduced pressure and the crude product (73% yield according to GC-MS data) was taken as such without further purification for the next synthetic step.

b). 2-Isopropyl-3-(2-methoxy-benzoylamino)-but-3-enoic acid methyl ester



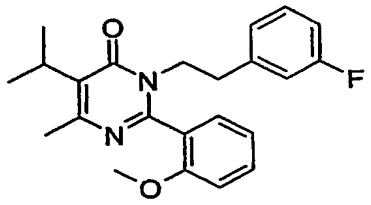
[0098] The crude 3-amino-2-isopropyl-but-3-enoic acid methyl ester of step 18a above in this method (5 g, 0.0318 mol) was dissolved in anhydrous THF (100 mL)

and anhydrous pyridine (5.2 mL, 0.0637 mol) was added. Anisoyl chloride (4.28 mL, 0.0318 mol) was added dropwise, and the mixture was refluxed for 2 hours. After cooling, water (100 mL) was added and the organic layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with 1N HCl (3 x 100 mL), water (100 mL), and brine (100 mL), dried over sodium sulfate and concentrated on a rotary evaporator. The product was purified by column chromatography over silica gel (200-400 mesh) eluting with 10% EtOAc/hexanes to give 2-isopropyl-3-(2-methoxy-benzoylamino)-but-3-enoic acid methyl ester (3 g, 33%) as a white powder.

[0099] ^{1}H NMR ($CDCl_3$): δ 0.93 (d, 3H, *J* = 6.6), 0.97 (d, 3H, *J* = 6.6), 2.10 - 2.23 (m, 1H), 2.73 (d, 1H, *J* = 11.1), 3.73 (s, 3H), 4.07 (s, 3H), 4.76 (d, 1H, *J* = 1.2), 6.09 (s, 1H), 7.00 (d, 1H, *J* = 8.1), 7.058 - 7.113 (m, 1H), 7.44 - 7.49 (m, 1H), 8.22 (dd, 1H, *J* = 1.8, 6), 9.96 (br s, 1H).

[00100] ^{13}C NMR ($CDCl_3$): δ 19.9, 21.0, 29.3, 51.9, 55.8, 60.7, 103.8, 111.4, 121.3, 121.8, 132.4, 133.0, 136.8, 157.4, 163.9, and 174.0.

c). 3-[2-(3-Fluoro-phenyl)-ethyl]-5-isopropyl-2-(2-methoxy-phenyl)-6-methyl-3H-pyrimidin-4-one

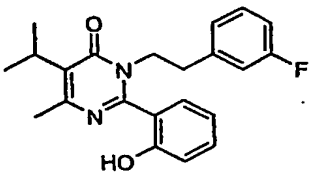


[00101] Phenyl magnesium bromide (1M solution in THF, 0.0021 mol) was added to a solution of 3-fluoro-phenethyl amine (0.27 mL, 0.0021 mol) in anhydrous toluene (20 mL). After stirring the mixture at 20°C for 10 min, 2-isopropyl-3-(2-methoxy-benzoylamino)-but-3-enoic acid methyl ester of step 18b above in this method (0.05 g, 0.0017 mol) was added. (Note that 2-isopropyl-3-(2-methoxy-benzoylamino)-but-3-enoic acid methyl ester or more generrically 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester provides another example of an appropriate carbamide for forming 2,3,5,6-Substituted 3*H*-Pyrimidin-4-ones once cyclized). The mixture was refluxed for 10 hours, cooled and ethyl acetate (50 mL) was added followed by 1N HCl (50 mL). The organic layer was separated and the aqueous layer was extracted

with EtOAc (3 x 50 mL). The combined organic extracts were washed with 1N HCl (3 x 100 mL), water (100 mL), and brine (100 mL). After drying over sodium sulfate and concentration on a rotary evaporator, the product was purified by column chromatography over silica gel (200-400 mesh) eluting with 12% EtOAc/hexanes to give 3-[2-(3-fluoro-phenyl)-ethyl]-5-isopropyl-2-(2-methoxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one (0.3 g, 46 %) as a white solid.

[00102] ^{1}H NMR δ 1.30 (d, 1H, *J* = 2.7), 1.31 (d, 1H, *J* = 2.7), 2.28 (s, 3H), 2.64 - 2.82 (m, 2H), 3.01 - 3.16 (m, 1H), 3.45 - 3.55 (m, 1H), 3.71 (s, 3H), 4.16 - 4.25 (m, 1H), 6.40 (td, 1H, *J* = 2.4, 9.6), 6.54 (d, 1H, *J* = 7.8), 6.87 - 7.08 (m, 4H), 7.35 - 7.41 (m, 1H).

d). 3-[2-(3-Fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one



[00103] A dry heavy-walled Pyrex tube was charged with 3-[2-(3-fluoro-phenyl)-ethyl]-5-isopropyl-2-(2-methoxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one of Example 18c (50 mg, 0.000132 mole), DMSO (5 mL) and sodium cyanide (65 mg, 10 equiv). The screw cap was tightened thoroughly. The reaction mixture was exposed to microwave irradiation at 180°C for 1 hour. The reaction mixture was allowed to reach room temperature and was carefully acidified with 50% HCl and extracted with ethyl acetate (3 x 25 mL). Caution, HCN may form. The combined organic extracts were washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude product, which was almost pure, was filtered through a short column packed with silica gel (200-400 mesh) using 25% EtOAc/hexanes to afford 35 mg (72%) of 3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one. ^{1}H and ^{13}C NMR spectral data of the compound were identical to those of the product prepared as described in Example 10.

[00104] It will be obvious to those having skill in the art that many changes may be made to the details of the above-described embodiments without departing from the underlying principles of the invention. The scope of the present invention should, therefore, be determined only by the following claims.

Claims

1. A method for preparing 2,3,5,6-Substituted 3*H*-Pyrimidin-4-ones comprising:

cyclizing an appropriate carbamide to obtain 2,3,5,6-Substituted 3*H*-Pyrimidin-4-ones.

2. The method as recited in claim 1, wherein the appropriate carbamide is an appropriate acetic acid 2-(1-alkyl-2-R^4-carbamoyl-alk-1-enylcarbamoyl)-phenyl ester.

3. The method as recited in claim 2, further comprising: acylation of an appropriate 3-amino-2-alkyl-alk-2-enoic acid R^4-amide to obtain the appropriate acetic acid 2-(1-alkyl-2-R^4-carbamoyl-alk-1-enylcarbamoyl)-phenyl ester.

4. The method as recited in claim 3, further comprising: reacting 2-alkyl-3-oxo-R^4-amide with anhydrous ammonia on catalysis by anhydrous aluminum chloride to obtain the appropriate 3-amino-2-alkyl-alk-2-enoic acid R^4-amide.

5. The method as recited in claim 4, further comprising: reacting 2-(2-alkyl-[1,3]dioxolan-2-yl)-*N*-R^4-alkanamide with *p*-toluenesulfonic acid monohydrate to obtain 2-alkyl-3-oxo-R^4-amide.

6. The method as recited in claim 5, further comprising: reacting 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid with oxalyl chloride followed by reaction with a primary amine to obtain 2-(2-alkyl-[1,3]dioxolan-2-yl)-*N*-R^4-alkanamide.

7. The method as recited in claim 6, further comprising: hydrolysis of 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid alkyl ester.

8. The method as recited in claim 7, further comprising: reacting of 2-alkyl-3-oxo-alkylic acid alkyl ester with ethylene glycol and *p*-toluenesulfonic acid monohydrate to obtain 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid alkyl ester.

9. The method as recited in claim 1, wherein the appropriate carbamide is an appropriate 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester.

10. The method as recited in claim 9, wherein the 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester is cyclized by reacting it with a primary amine and the Grignard reagent.

11. The method as recited in claim 9, wherein the 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester is obtained by acylation of an appropriate 3-amino-2-alkyl-but-3-enoic acid methyl ester.

12. The method as recited in claim 11, wherein the appropriate 3-amino-2-alkyl-but-3-enoic acid methyl ester is obtained by reacting 2-alkyl-3-oxo-butyric acid methyl ester with liquid ammonia.

13. The method as recited in claim 1, wherein the appropriate carbamide is 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester.

14. The method as recited in claim 13, wherein the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester is cyclized by reacting 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester with phenylmagnesium bromide and primary amine.

15. The method as recited in claim 13, wherein cyclizing the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester yields 2-(2-alkoxy-phenyl)-3-R^4-5,6-dialkyl-3*H*-pyrimidin-4-ones, and

wherein the method further comprises reacting 2-(2-alkoxy-phenyl)-3-R^4-5,6-dialkyl-3*H*-pyrimidin-4-ones with sodium cyanide under microwave irradiation to yield 3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one.

16. The method as recited in claim 13, wherein the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester is obtained by reacting 2-alkyl-3-oxo-butyric acid alkyl ester with liquid ammonia.

17. The method as recited in claim 1, wherein the 2,3,5,6-Substituted 3*H*-Pyrimidin-4-ones is at least one of:

2-(2-hydroxy-phenyl)-5,6-dimethyl-3-phenethyl-3*H*-pyrimidin-4-one;

3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

3-[2-(4-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

5-ethyl-2-(2-hydroxy-phenyl)-6-methyl-3-phenethyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(4-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-5-propyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-methoxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-5-methyl-3-phenethyl-6-trifluoromethyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-3-phenethyl-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one;

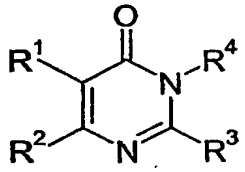
3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one;

5-cyclopropyl-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-3-phenethyl-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one; and

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one.

18. The method for preparing a compound having the chemical formula:



wherein:

R^1 and R^2 are either independently one of: H, halogen, CN, CF_3, lower alkyl, cycloalk, aryl; or R^1 and R^2 are together $-(CH_2)_n-$ and n is 5, 4, or 3;

R^3 is aryl group, which may have 1 to 4 substituents in the aryl ring each selected from the group consisting of: H, halogen, CN, CF_3, OCF_3, lower alkyl, N(lower alkyl)$_2$, lower alkoxy, OH, OC(O)-lower alkyl, OC(O)-lower alkylamino, and OC(O)-lower alkyl-N(lower alkyl)$_2$;

R^4 is H, lower alkyl, or a group of the formula $-(CH_2)_n-R^5$ wherein n is 0, 1, or 2, and

R^5 is an aryl group which may have 1 to 3 substituents on the aryl ring each selected from the group consisting of: H, halogen, CN, CF_3, OCF_3, lower alkyl, lower alkoxy, NH-lower alkyl, NH-alkylaryl, N(lower alkyl)$_2$, OH, OC(O)-lower alk, OC(O)-lower alkylamino, and OC(O)-lower alkyl-N(lower alk)$_2$;

and pharmaceutically acceptable salts or complexes;

comprising: cyclizing an appropriate carbamide to yield the compound.

19. The method as recited in claim 18, wherein the appropriate carbamide is an appropriate acetic acid 2-(1-alkyl-2-R^4-carbamoyl-alk-1-enylcarbamoyl)-phenyl ester.

20. The method as recited in claim 19, further comprising: acylation of an appropriate 3-amino-2-alkyl-alk-2-enoic acid R^4-amide to obtain the appropriate acetic acid 2-(1-alkyl-2-R^4-carbamoyl-alk-1-enylcarbamoyl)-phenyl ester.

21. The method as recited in claim 20, further comprising: reacting 2-alkyl-3-oxo-R^4-amide with anhydrous ammonia on catalysis by anhydrous aluminum chloride to obtain the appropriate 3-amino-2-alkyl-alk-2-enoic acid R^4-amide.

22. The method as recited in claim 21, further comprising: reacting 2-(2-alkyl-[1,3]dioxolan-2-yl)-*N*-R^4-alkanamide with *p*-toluenesulfonic acid monohydrate to obtain 2-alkyl-3-oxo-R^4-amide.

23. The method as recited in claim 22, further comprising: reacting 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid with oxalyl chloride followed by reaction with a primary amine to obtain 2-(2-alkyl-[1,3]dioxolan-2-yl)-*N*-R^4-alkanamide.

24. The method as recited in claim 23, further comprising: hydrolysis of 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid alkyl ester.

25. The method as recited in claim 24, further comprising: reacting of 2-alkyl-3-oxo-alkylic acid alkyl ester with ethylene glycol and *p*-toluenesulfonic acid monohydrate to obtain 2-(2-alkyl-[1,3]dioxolan-2-yl)-alkanoic acid alkyl ester.

26. The method as recited in claim 18, wherein the appropriate carbamide is an appropriate 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester.

27. The method as recited in claim 26, wherein the 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester is cyclized by reacting it with a primary amine and the Grignard reagent.

28. The method as recited in claim 26, wherein the 3-R^3-carbamoylamino-2-alkyl-but-3-enoic acid methyl ester is obtained by acylation of an appropriate 3-amino-2-alkyl-but-3-enoic acid methyl ester.

29. The method as recited in claim 28, wherein the appropriate 3-amino-2-alkyl-but-3-enoic acid methyl ester is obtained by reacting 2-alkyl-3-oxo-butyric acid methyl ester with liquid ammonia.

30. The method as recited in claim 18, wherein the appropriate carbamide is 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester.

31. The method as recited in claim 30, wherein the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester is cyclized by reacting 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester with phenylmagnesium bromide and primary amine.

32. The method as recited in claim 30, wherein cyclizing the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester yields 2-(2-alkoxy-phenyl)-3-R^4-5,6-dialkyl-3*H*-pyrimidin-4-ones, and

wherein the method further comprises reacting 2-(2-alkoxy-phenyl)-3-R^4-5,6-dialkyl-3*H*-pyrimidin-4-ones with sodium cyanide under microwave irradiation to yield 3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one.

33. The method as recited in claim 30, wherein the 2-alkyl-3-(2-alkoxy-benzoylamino)-but-3-enoic acid methyl ester is obtained by reacting 2-alkyl-3-oxo-butyric acid alkyl ester with liquid ammonia.

34. The method as recited in claim 18, wherein the 2,3,5,6-Substituted 3*H*-Pyrimidin-4-ones is at least one of:

2-(2-hydroxy-phenyl)-5,6-dimethyl-3-phenethyl-3*H*-pyrimidin-4-one;

3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

3-[2-(4-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6-dimethyl-3*H*-pyrimidin-4-one;

5-ethyl-2-(2-hydroxy-phenyl)-6-methyl-3-phenethyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

5-ethyl-3-[2-(4-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-5-propyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-methoxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-isopropyl-6-methyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-5-methyl-3-phenethyl-6-trifluoromethyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-3-phenethyl-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5,6,7,8-tetrahydro-3*H*-quinazolin-4-one;

5-cyclopropyl-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-pyrimidin-4-one;

2-(2-hydroxy-phenyl)-3-phenethyl-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one; and

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3,5,6,7-tetrahydro-cyclopentapyrimidin-4-one.

35. The method as recited in claim 18, wherein R^1 and R^2 are each lower alkyl.

36. The method as recited in claim 35, wherein said lower alkyl is one of methyl, ethyl, propyl, cyclopropyl and isopropyl.

37. The method as recited in claim 35, wherein R^2 is methyl.

38. The method as recited in claim 18, wherein R^1 and R^2 together are $-(CH_2)_n-$ and wherein n is 4 or 3.

39. The method as recited in claim 18, wherein R^1 and R^2 together are at least one of $-(CH_2)_4-$ and $-(CH_2)_3-$.

40. The method as recited in claim 18, wherein R^3 is phenyl optionally substituted with hydroxy.

41. The method as recited in claim 18, wherein

R^4 further comprises the group $-(CH_2)_n- R^5$;

wherein n is 1 or 2; and

R^5 is phenyl optionally substituted with 1 or 2 halogens.

42. The method as recited in claim 41, wherein n is 2 and said halogens are one of fluorine and chlorine.